II. REMARKS

A. Status of the Claims

Claims 38, 47 and 49-65 were amended without prejudice or admission.

New claims 66-73 were added.

Applicants submit that support for the amended and new claims can be found as follows.

Support for "a therapeutically effective amount of a COX-2 inhibitor together with a dose of an opioid analgesic" in claim 38 can be found, e.g., on page 9, lines 13-15, of the specification and page 15, lines 14-23, of U.S. application Serial No. 60/059,195 ("the provisional application") ("[t]he present invention encompasses a method of inhibiting COX-2 and treating COX-2 mediated diseases comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of the COX-2 inhibitor and opioid analgesic combination of the present invention ...").

Support for the COX-2 inhibitor being N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide ("T-614") and the opioid analgesic being oxycodone in claims 38, 53 and 62 can be found, e.g., in Table I of the original specification and the provisional application and claim 20 of the provisional application ("[t]he pharmaceutical composition according to claim 1, wherein said opioid analgesic is ... oxycodone ... and ... COX-2 inhibitor is ... T614").

Support for "the COX-2 inhibitor ... combined with carrier materials in a single dosage form" in claim 38 can be found, e.g., on page 18, lines 21-24, of the original specification ("[t]he amount of COX-2 inhibitor that may be combined with the carrier materials to produce a single dosage form having COX-2 inhibitor and opioid analgesic ..."), page 11, lines 4-6, of the original specification and page 7, line 21, to page 8, line 5, of the provisional application ("... the

oral solid dosage form include a sustained release carrier which causes the sustained release of the opioid analgesic, or both the opioid analgesic and the COX-2 inhibitor ...").

Support for "25 mg of the COX-2 inhibitor" in claims 47, 63 and 68 and "50 mg of COX-2 inhibitor" in claims 50, 65 and 69 can be found, e.g., on page 18, line 28, of the original specification and page 11, line 17, of the provisional application ("[u]nit dosages will generally contain between from about 0.5 mg to about 1500 mg of a COX-2 inhibitor, and typically 25 mg, 50 mg ...).

Support for "an oral dosage form consisting of (i) a COX-2 inhibitor in an immediate release form; (ii) an opioid analgesic in a sustained release form; and (iii) and at least one pharmaceutically acceptable excipient" in claim 53 can be found, e.g., on page 24, line 31, to page 25, line 1, of the original specification and page 19, lines 8-9, of the provisional application specification ("[t]he sustained release dosage form may include the opioid analgesic in sustained release form and COX-2 inhibitor ... in immediate release form ...").

Support for "administered 2 times per day" in claim 54 can be found, e.g., on page 20, lines 29-32, of the original specification, and page 13, lines 23-26 of the provisional application ("[a] composition comprising any of the above-identified combinations of opioid analgesics and COX-2 inhibitors may be administered in divided doses ranging from 2 to 6 times per day ...").

Support for "COX-2 inhibitor in an immediate release form ... coated onto a tablet comprising the opioid analgesic in the sustained release form" in claim 59 can be found, e.g., on page 24, line 31, to page 22, line 8, of the original specification, and page 8, lines 16-17 ("... the tablet contains the opioid analgesic within a sustained release matrix and COX-2 inhibitor coated into the tablet into as an immediate release layer.").

Support for "a combination of a COX-2 inhibitor and an opioid analgesic in an admixture of excipients" in claim 62 can be found, e.g., on page 23, lines 4-30, of the original specification and page 16, line19, to page 17, line 5, of the provisional application ("[t]he combination of

COX-2 inhibitor and an opioid analgesic can be employed in admixtures with conventional excipients ...").

Support for "administered once-daily" in claim 61 can be found, e.g., on page 22, line 29-30, of the original specification and page 16, lines 14-16, of the provisional application ("[t]he combination of COX-2 inhibitor and oral opioid analgesics may be formulated to provide for an increased duration of analgesic action allowing once-daily dosing ...").

Support for "a sustained release carrier which provides a sustained release of the COX-2 inhibitor" in claim 64 can be found, e.g., page 11, lines 4-6, of the original specification and page 7, line 21, to page 8, line 5, of the provisional application ("... the oral solid dosage form include a sustained release carrier which causes the sustained release of ... the opioid analgesic and the COX-2 inhibitor ...").

Support for "a solid dosage form" in claims 66, 70 and 72 can be found, e.g., on page 11, line 4, of the original specification and page 7, lines 21-22, of the provisional application (".. the invention comprises an oral solid dosage form ...").

Support for "a tablet" in claims 67, 71 and 73 can be found, e.g., on page 25, lines 26-28, of the original specification and page 8, lines 19-20, of the provisional application ("[t]he oral pharmaceutical compositions containing the inventive combination of drugs ... may be in the form of tablets ...").

Claims 38 and 47-73 will be pending once the present amendment is entered.

Applicants submit that claims 38 and 47-73 encompass the elected species.

B. Priority

In the Office Action, the Examiner stated that "[t]he instant application, 10/057,632 filed 1/25/2002 claims priority as a CON of application 09/154,354 filed 09/17/1998 (now PAT 6,552,031) which claims benefit of provisional application 60/059,195 filed 09/17/1997" and asserted that certain limitations of the pending claims are not disclosed in the earlier applications. Office Action, page 3.

Applicants respectfully disagree with the Examiner's assertion and submit that the elements of the examined claims are disclosed in the earlier applications, and that the present application is entitled to the September 17, 1997 priority date.

Applicants submit that support for a method for effectively treating pain in humans with an oral dosage form comprising N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide, oxycodone and carrier materials can be found, e.g., on page 9, lines 13-15, of the '354 application and page 15, lines 14-23, of U.S. application Serial No. 60/059,195 ("the provisional application") ("[t]he present invention encompasses a method of inhibiting COX-2 and treating COX-2 mediated diseases comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of the COX-2 inhibitor and opioid analgesic combination of the present invention ..."). Support for the COX-2 inhibitor being N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide and the opioid analgesic being oxycodone in claims 38, 53 and 62 can be found, e.g., in Tables I of the '354 application and the provisional application, and claim 20 of the provisional application ("[t]he pharmaceutical composition according to claim 1, wherein said opioid analgesic is ... oxycodone ... and ... COX-2 inhibitor is ... T614").

Applicants submit that support for "a pharmaceutically acceptable salt of oxycodone in a sustained release form" can be found, e.g., on page 24, lines 25-30, of the '354 application and page 18, line 24, to page 19, line 7, of the provisional application ("The COX-2 inhibitor and opioid analgesic combination can be formulated a controlled release oral formulation").

Applicants respectfully note that "[t]he term "opioid analgesic" is defined [, on page 12 of the '354 application] ... as the drug in its base form, **or a pharmaceutically acceptable salt** or complex thereof." Applicants therefore submit that the term "opioid analgesic" encompasses pharmaceutically acceptable salts of opioid analgesics. Applicants further submit that both the '354 application and the provisional application disclosed oxycodone as one of the opioid analgesics suitable for use in the presently claimed methods. See, e.g., page 18, lines 6-8, of the '354 application and page 10, lines 19-21, of the provisional application ("[i]n certain preferred embodiments, the opioid analgesic is ... oxycodone ...").

Applicants submit that support for "once-a-day administration" of the disclosed opioid analgesics can be found, e.g., on page 22, line 30, of the '354 application and page 16, line 15, of the provisional application ("[t]he combination of COX-2 inhibitor and oral opioid analgesic may be formulated to provide for an increased duration of analgesic action allowing once-daily dosing.").

Applicants submit that support for a pharmaceutically acceptable salt of oxycodone with a sustained release carrier such as alkylcellulose can be found, e..g., on page 26, lines 27-30, of the '354 application and page 21, lines 18-20, of the provisional application ("... the substrate ... containing the opioid analgesic (with or without the COX-2 inhibitor) is coated with ... alkylcellulose ..."). As stated above, the term "opioid analgesic" encompasses pharmaceutically acceptable salts of the opioid analgesic, and oxycodone is one of the disclosed opioid analgesics.

Applicants submit that support for "dosage forms using a pharmaceutically acceptable salt of oxycodone in a sustained release form with particles from about 0.1 mm to about 2.5 mm or from about 0.5 mm to about 2 mm" can be found, e.g., on page 25, lines 14-17, of the '354 application and page 19, lines 21-24, of the provisional application ("... the sustained release dosage form comprises ... particles containing or comprising the active ingredient, wherein the particles have diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm"). Applicants submit that it clear from the specifications of the earlier application

that "the active ingredient" encompasses a pharmaceutically acceptable salt of oxycodone. See, e.g., page 8, lines 6-8, of the '354 application.

Applicant submit that "T-614 being coated onto a tablet comprising oxycodone plus a sustained release carrier" is supported, e.g., on page 24, line 31, to page 25, line 6, and on page 8, lines 16-17, of the provisional application ("... the tablet contains the opioid analgesic within a sustained release matrix and the COX-2 inhibitor coated into the tablet as an immediate release layer..."). As stated above, the earlier applications support opioid analgesic being oxyocodone and the COX-2 inhibitor being T-614.

Applicant submit that "a sustained release carrier incorporated into a matrix with oxycodone" is supported, e.g., on page 24, lines 28-30, of the '354 application ("[t]he sustained release dosage form may optionally include a sustained release carrier which is incorporated into a matrix along with the opioid, or which is applied as a sustained release coating").

Applicants submit that "sustained release of T-614" is supported, e.g., on page 25, line 1, of the '354 application and page 19, line 9, of the provisional application ("COX-2 inhibitor in sustained release form.").

For the foregoing reasons, Applicants submit that the pending claims are supported by the earlier applications.

C. Rejection- 35 U.S.C. § 103

Claims 38, 47-52 and 53-65 were rejected under 35 U.S.C. § 103(a) over the Baker patent, the Tanaka publication, in view of U.S. Patent No. 5,472,712 to Oshlack et al. and U.S. Patent No. 6,294,195 to Oshlack et al..

The rejection is respectfully traversed for the reasons presented in the response filed on June 11, 2009, hereby incorporated by reference, and the reasons presented below.

Independent claims 38, 53 and 62 are directed in part to a method of treating pain by administering to a human patient N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide ("T-614") in combination with oxycodone as recited in these claims.

Applicants respectfully submit that the cited references (alone or in combination) do not teach or suggest that T-614 may be administered to human patients together with an additional analgesic agent (i.e., oxycodone), e.g., because the Tanaka publication describe administration of T-614 animals by itself, without any additional active agents, and does not describe administration of T-614 to humans.

In response to the Examiner's statement on page 6 of the Office Action that "Tanaka et al. teaches T-614 is effective against arthritis in figure 4, reading on amended claim 38 as well as new claims 56 and 62" and on page 8 of the Office Action that it is shown in "figure 4 of Tanaka et al where it is shown that T-614 is effective against arthritic pain," Applicants respectfully submit that Table 4 of the Tanaka publication depicts results from the experiment in which anti-inflammatory activity of T-614 was investigated, rather than analgesic activity. Applicants respectfully note that the experiment was done on rats, rather than humans. Accordingly, Applicants submit that the purported teaching of the Tanaka reference does not read on claims 38, 56 and 62, which are directed to a method of treating pain and recite a step of administering T-614 to a human patient.

In response to the Examiner's statement on page 12 of the Office Action that "evidence regarding predictability is provided by Beaver (1984 Combination Analgesics. The American Journal of Medicine pp 38-53) and Beaver II (1992 Evaluation and Treatment of Chronic Pain Ch 29 Nonsteroidal anti-inflammatory analgesics and their combination with opioids), showing the idea of predictably combining NSAIDs with opioids was well established in the art at the time the presently claimed invention was made," Applicants note that the 1984 Beaver Article states on page 38, e.g., that "**[u]nless** there is sufficient evidence that use of an analgesic combination is likely to yield therapeutic results unobtainable with a suitable dose of one of its

constituents, **a single analgesic alone should be used**." (emphasis added). Applicants further note that the 1992 Beaver article states on page 378, e.g., that "**[i]f** an optimal regimen of an NSAID alone does not provide adequate analgesia, one can add a weak opioid to the existing NSAID regimen."

Applicants submit that administration of T-614 to humans is not described in the cited references. Applicants further submit that there is nothing in the cited references that indicates that administration of T-614 alone to animals will not provide adequate analgesia. Therefore, Applicants submit that, in accordance with the guidance provided by the Beaver articles, a skilled person would not have been motivated by the cited references to administer T-614 together with an additional analgesic agent (i.e., oxycodone) to humans.

Accordingly, Applicants submit that the combination of the cited references does not render claims 38, 53 and 62 and their dependent claims obvious.

With further regard to claims 47, 50, 63 and 65, Applicants submit that the combination of the cited references does not teach or suggest administering 25 mg or 50 mg of T-614 to humans as recited in these claims. Applicants respectfully note that in the cited references T-614 was administered to animals, rather than humans. Applicants further submit that there is no disclosure in the cited references of how to convert the animal doses of T-614 described therein to human doses. Accordingly, Applicants respectfully submit that claims 47, 50, 63 and 65 are not rendered obvious by the combination of the cited references for this additional reason.

In response to the Examiner's reliance on *In re Aller* on page 6 of the Office Action, Applicants note that the claims at issue in *In re Aller* did were not directed to a method of treating pain, and, therefore, respectfully submit that the Examiner's reliance on *In re Aller* may be inappropriate.

In response to the Examiner reliance on *In re Kerkhoven* on page 7 of the Office Action, Applicants respectfully note claims *In re Kerkhoven* were not directed to a method of treating

pain. According to the MPEP, in *In re Kerkhoven* "[c]laims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious." MPEP, section 2144.05. Accordingly, Applicants respectfully submit that the Examiner's reliance on *In re Kerkhoven* may also be inappropriate.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

With regard to new claims 66-73, Applicants respectfully submit that the cited references do not teach or suggest that T-614 may be administered in a solid dosage form (e.g., a tablet) as recited in these claims. Applicants respectfully note that the Tanaka reference (which has been relied upon by the Examiner for the teaching of T-614) describes administration of T-614 in the form of a suspension, rather than a solid dosage form. See, e.g., page 936 ("[t]he test compounds were suspended in 0.5% sodium carboxymethylcellulose (CMC) solution."). Therefore, Applicants submit that claims 66-73 are not rendered obvious for this additional reason.

D. Rejection- 35 U.S.C. § 112

Claims 38 and 47-65 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as failing to comply with the written description requirement.

The rejection is respectfully traversed.

Applicants respectfully submit that claims 38 and 47-65 are supported by the original specification and that believe that the rejection has been rendered moot by the amendment to the claims. Support for the claims can be found, e.g., as submitted above in the Status of the Claims and Priority sections.

Withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview may advance the prosecution of the application.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Oleg Ioselevich
Reg. No. 56,963

DAVIDSON, DAVIDSON & KAPPEL, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940